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ORIGINAL ARTICLE

Effect measure modification conceptualized using selection diagrams as mediation by mechanisms of varying population-level relevance

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Abstract

Objectives: We are often confronted in public health by associations that vary by population or subpopulation. Much effort has focused on the statistical and biological interpretation of such effect measure modification (EMM) because of the importance to public health. However, EMM remains difficult to conceptualize because it apparently violates everyday understanding of causes as usually acting consistently, making it difficult to predict when EMM may occur and raises questions about how to determine the external validity of interventions without extensive retesting by population or subpopulation.

Study Design and Setting: Methods exposition.

Results: We propose that EMM can be thought of as mediation of an intervention (or exposure) on outcome by mechanism(s) whose relevance differs between population groups, which can be illustrated in causal diagrams, that is, directed acyclic graphs and selection diagrams, meaning external validity can be formally considered as mediation according to ''selection variables.'' EMM can then be represented graphically and its consequences predicted.

Conclusion: This new conceptualization of EMM transforms EMM from a concept that violates everyday understanding of causes into an insight generating means of thinking about interventions (or exposures) in terms of their mediating mechanism(s) and corresponding population- or subpopulation-specific attributes to help target interventions effectively.

Keywords: Effect measure modification; Mediation; Selection diagram; External validity; Generalizability; Mechanism

1. Introduction

The ongoing methodological ''revolution'' in research methods has deconstructed paradoxes [1], such as the obesity paradox [2−4] and clarified the conditions required for unbiased assessment of causal effects [5]. It has also drawn attention to the importance of assessing effects within a theoretical model, to inform identification of confounders and potential sources of selection bias [6]. However, the conditions required to identify whether an effect measure is sample specific or has external validity, that is, is generalizable to the full target population (including the study sample) or transportable to a new population are not so clear [7−11], particularly as treatments may be complex [12], and effects may vary by subgroup, that is, effect measure modification (EMM). The presence of EMM and different distributions of effect measure modifiers in the study sample, the target population, and new population is one reason why an effect may not extend beyond the study sample, meaning that external validity and EMM are linked concepts.

Extensive consideration has been given to the possibility that associations of exposure with outcome may vary between populations or by subpopulation [7,8,11], usually defined as heterogeneity of an estimated causal effect of one exposure across levels of one or more other conditions at the population or subpopulation level [7,8,11]. Comprehensive methods to assess and classify EMM, both on additive and multiplicative scales, are now well established

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What is new?

Key findings

- Re-conceptualizing effect measure modification as mediation by mechanism(s) whose relevance varies by specific group attributes (selection factors) can explain heterogenity and address external validity.
- Use of selection diagrams allows clear graphical representation of effect measure modification.

What this adds to what was known?

- Effect measure modification can be shown on causal diagrams.

What is the implication and what should change now?

- Effect modifiers should be replaced by explicit identification of specific selection factors and mediating mechanisms.
- Selection diagrams should be used to represent effect measure modification.

[13,14]. Additive scales correspond to risk differences and hence are more directly relevant to the effects of interventions on public health [11], whereas multiplicative scales are more mathematically amenable but may obscure important differences [15]. However, identification of the circumstances in which such heterogeneity might occur to help public health practitioners design appropriate population-level interventions is not always easy. Here, we consider, with examples, in the context of current understanding, whether the application of selection diagrams [16] could help further elucidate EMM, particularly on an additive scale, thereby strengthening our understanding of external validity.

2. Sufficient-component cause model

Rothman's sufficient-component cause model has been immensely important in drawing attention to the multifactorial and interactive nature of the factors determining health [17]. The depiction in terms of "causal pies" illustrates the role of different combinations of different factors (Fig. 1) [11]. Specific causes may be either present or absent in an individual, so that the magnitude of the effect estimate for a particular component cause in a population is a function of the distribution of persons in the population who have all the other component causes complete and for whom the particular component can cause disease. The sufficient-component causal model has also been extended to provide a conceptual framework for the assessment of mediation [18], along with the recognition that "background factors" are involved in activating different mediating mechanisms [19,20]. These helpful developments have largely focused on classifying, decomposing, and estimating in the context of exposure mediator interaction [21–23] rather than elucidating and representing the background factors that may result in EMM. However, explicit identification of these "background factors" or population (or subpopulation) attributes and distinguishing them from the mediating mechanism is vital to the effective implementation of interventions across different populations. The sufficient-component cause model indicates that when assessing the causal effect of exposure on outcome, other likely population-related attributes are important in identifying which causal pie is appropriate. Despite this important conceptual insight, the sufficient-component cause model has not yet yielded an analytic means of quantifying how these factors work together [24,25]. Specifically, it does not provide an explicit framework for separating the mediating mechanism(s) of an intervention (or exposure) on outcome from the attributes in a given population that determine whether the mechanism(s) are relevant or not. To illustrate, we provide motivating examples.

2.1. Illustrative examples

One example concerns sunscreen and skin cancer. Sunscreen prevents skin cancer by protecting against sunburn. Given existing knowledge about sunburn, we can infer that sunscreen will be a more effective intervention for skin cancer prevention in a sunny place for populations prone to sunburn, making skin tone a relevant "background factor." Sunburn is the mediating mechanism and skin tone is an attribute that could classify the population into subgroups

Fig. 1. Illustration of three causal pies making up a sufficient-component causal "pie" model [11].

where the sunscreen intervention has different effects. Alternatively, several mediating mechanisms for the effect of an intervention (or exposure) on outcome could exist. A dietary restriction intervention in a population with a high prevalence of adiposity will reduce diabetes incidence by reducing the adipose component of body mass index [26]. The same dietary restriction intervention might be less successful for diabetes prevention in a thin population but could instead increase incidence of diabetes if it reduced the muscle mass that may protect against diabetes [27]. Here, weight loss is the mediating mechanism for the intervention, and body composition is an attribute that classifies the population into subgroups where the same intervention might have different effects.

3. Structural causal models

Representation of sufficient-component cause models using directed acyclic graphs (DAGs) [28] has facilitated explicit representation of the researcher's understanding of major causal influences, to inform analysis and collection of new data. DAGs are illustrative, simplified models of reality which, at an operational level, help determine whether the effect of an intervention is identifiable from data. DAGs can also be represented in terms of mathematical expressions for causal effects in terms of conditional independences and observed distributions [16,28]. If no appropriate data for testing the model exist, DAGs can help identify what data are required [16,28]. DAGs allow researchers to make the assumptions underlying their proposed model explicit and to understand whether these assumptions are sufficient to obtain consistent estimates [28]. Use of DAGs has facilitated clear communication of complex models describing relations between exposure and outcome, as well as other relevant factors, such as confounders, mediators, and factors determining selection into the study. However, a key limitation of DAGs is that EMM is difficult to represent or model [19,20,29]. Several important innovations have been made to address this issue. EMM has been classified as direct, indirect, by proxy, and by common cause, according to how the effect modifier relates to the outcome [14]. EMM has been represented as two causes converging before affecting the outcome [30]. EMM has also been represented using single world intervention graphs [31]. However, none of these clearly make the conceptual distinction been a causal factor and attributes that determine its relevance in a specific setting. Figure 2A shows that DAGs clearly demonstrate the causal pathway of X (exposure) to Y (outcome), but difficulties have been experienced in representing EMM (Z) in a DAG [29].

These issues raise the question as to how a DAG could illustrate that, on average, attributes of the population are relevant to the effects of an intervention on population health, as in Fig. 2, even without confounding or selection bias. We need to illustrate how the EMM occurs, by showing the sources of EMM in the DAG, which we suggest can be represented using selection diagrams [5,16] to make the attributes driving EMM explicit and separate from any mediating mechanisms.

4. Reconceptualization of EMM

One way of conceptualizing EMM is as depending on the relevance of potential mediating mechanism(s) by which an intervention or exposure operates on the outcome in different populations or population subgroups, meaning the same intervention or exposure can have varying effects on the same outcome. At its simplest, this is a DAG with a mediator between the exposure and outcome, whose relevance may vary between populations or population subgroups and thus explains why the exposure may have varying effects in different groups (Fig. 3A). This conceptualization goes beyond previous conceptualizations [14], by including a mediating mechanism to make the means by which EMM occurs explicit. Essentially, this is the application of selection diagrams to display what sufficient-component causal models and DAGs have not clearly illustrated and distinguished thus far—how the modifier influences the association of exposure with outcome [16,28]. Selection diagrams specifically include "S-variable(s)" or selection factors, that is, background factors or attributes that vary by population (or population subgroup) by which "structural discrepancies between the two populations are suspected to take place" [16]. This conceptualization is similar to the concept of "causal

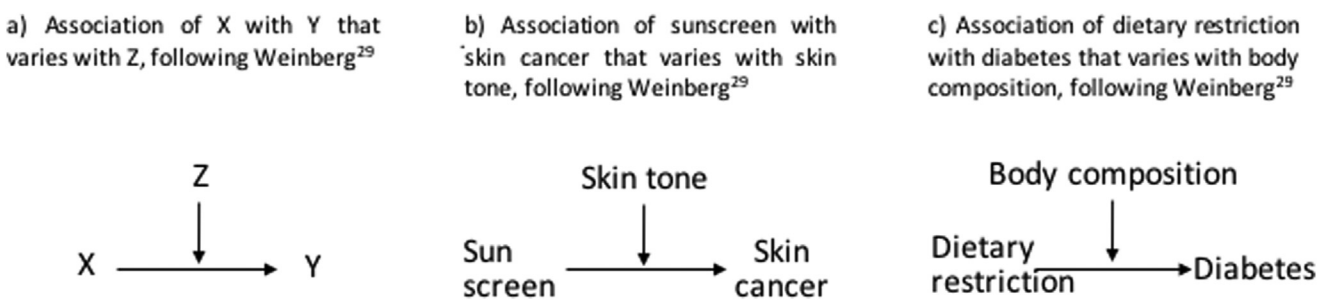
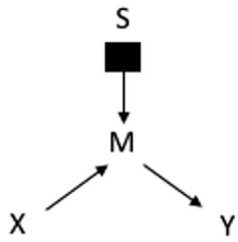
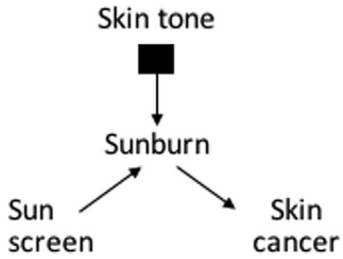


Fig. 2. Illustration of effect measure modification in directed acyclic graphs following Weinberg [29].

a) Simple example of Pearl's selection diagram, X is the exposure or intervention, Y is the outcome, M is the mediator and S is the selection factor



b) Example 1: DAG depicting sunscreen intervention where the effect on skin cancer is mediated by sunburn whose relevance depends on the skin tone of the relevant population.



c) Example 2: DAG depicting dietary restriction intervention where the effect on diabetes is mediated by fat and/or muscle loss whose effect on diabetes depends on the body composition of the relevant population.

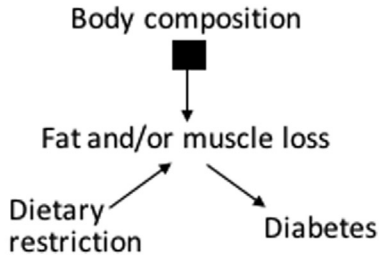


Fig. 3. Effect measure modification depicted using Pearl's selection diagrams, S-variables, i.e., selection factors, are indicated by a square at the start of the arrow shaft [5,16].

interaction'' defined as ''Causal interactions refer to settings in which there are persons for whom the outcome would occur (by a certain time) if both exposures were present but for whom the outcome would not occur if only one of the two exposures were present'' [32]. However, this conceptualization here makes it explicit that causes act via mechanisms and that the factors determining different associations of an exposure with an outcome should be explicitly identified and represented using selection diagrams. Once EMM is conceptualized as structural factors resulting in population or population subgroup-specific mediating mechanisms, then it can be represented by the use of DAGs with selection diagrams to make the reasons for EMM explicit and thereby facilitate explanation and planning of public health interventions. Illustrations based on the previous examples are provided below (Fig. 3).

4.1. Sunscreen and skin cancer

It is well known that people with lighter skin tones are more likely to experience sunburn than people with darker skin tones and that sunburn leads to skin cancer. In the same climate, an intervention promoting the use of sunscreen to reduce skin cancer at the population level would be expected to have a larger absolute effect in population subgroups with a large proportion of people with light skin tones than in population subgroups where people have darker skin tones. Using the terminology of selection diagrams [16], the population subgroup attribute of skin tone is the ''S-variable'' which determines whether the intervention of sunscreen reduces skin cancer acting via the mediating mechanism or ''M-variable'' of sunburn, as shown in Fig. 3B. In this situation, EMM might be observed for a range of attributes, such as race or ethnicity, which might or might not correspond to the population attribute determining the effectiveness of the intervention. Explicit identification of the M-variable, here sunburn, and the S-variable, here skin tone, provides explicit representation of an identifiable underlying model thereby allowing estimation of the causal effect of the sunscreen intervention in a new population by using the transport formula [5].

4.2. Dietary restriction and diabetes

Weight loss in obese people reduces the risk of diabetes by reducing adiposity [27], but weight loss in thin people might increase the risk of diabetes by reducing muscle mass [26], so a dietary restriction intervention in different populations may yield different results. Using the terminology of selection diagrams, the population attribute of body composition is the ''S-variable'' which determines whether the dietary restriction intervention has a beneficial effect by reducing adiposity or a harmful effect by reducing muscle mass [28]. Here, the mediating mechanism (weight loss) by which the dietary restriction intervention operates differs in these two population subgroups (obese vs. thin) because it has two different biological mediators or M-variables of adipose tissue or muscle mass. Different population-specific mediators for the same intervention mean dietary restriction can protect against diabetes by reducing fat mass or cause diabetes by reducing muscle mass (Fig. 3C). Thus, a dietary restriction intervention could have different effects on diabetes in population groups defined by body composition. In this situation, EMM might be observed for a range of attributes, such as race/ethnicity or socioeconomic position, which might or might not correspond to the population attribute determining the effectiveness of the intervention. As such, explicit identification of the M-variables, here fat and muscle, and the S-variable, here body composition, enables effective application of the dietary restriction intervention because effects in different populations can be estimated.

The key step for researchers and public health practitioners is to identify the potential mediators (the mediation variables(s) M) by which an exposure or intervention operates and the background factor(s) determining relevance in

a given population (the selection variable(s) (S)) so as to identify how public health interventions may operate in different populations. If the mediator(s) are known, they should be used to inform where an intervention would be effective, using the transport formula to estimate effects for populations with different attributes, that is, S-variables [5].

5. Discussion

Reconceptualization of EMM as one or more mediators of an intervention (or exposure) whose relevance may vary between populations or population subgroups enables the reasons for EMM to be made explicit in a manner that can be clearly represented (in DAGs with selection diagrams) within an axiomatic and logical structure for identifying effects. This conceptualization makes it explicit that effects may differ between populations, not because causes act inconsistently, but because of structural differences between populations, which affects the relevance of potential mediating mechanisms and whose identification can inform optimal use of an intervention. It also builds on the sufficient-component cause model by making explicit in what circumstances different components may be relevant.

Despite the power of this new conceptualization of EMM, it may not apply in all circumstances. First, apparent EMM may arise from confounding or selection bias, which should be eliminated rather than taken as an indicator of the need for different interventions in different groups. For example, stratification by age may result in different associations of exposure with outcome, but this heterogeneity might be due to confounding by overall health status, a factor moderately dependent on age that frequently causes many population-level exposures and outcomes [33,34]. Similarly, selection bias due to selective survival before recruitment is an age-associated phenomenon that may generate different associations by age. For example, the effect of smoking on dementia may look spuriously protective among the elderly because those who had previously died from smoking are automatically excluded from the study [35]. Second, a reconceptualization of EMM should be framed at the population level, not at the individual level [36]. For example, at the individual level, lung cancer may or may not occur in an active smoker, dependent on many factors, potentially including genetic predisposition and cumulative exposure, but at the population level, all else being equal lung cancer will have higher incidence in a smoking population than in a nonsmoking population. Correspondingly, the optimum intervention for an individual might differ from the optimum intervention for a community with a high prevalence of lung cancer resulting from a high proportion of active smokers. Third, EMM may not always act via a mediator. A varying baseline risk would generate EMM even without mediators. However, such a situation would beg the question as to why the baseline risk varied, which might best be explicitly addressed by identifying the mediating mechanism(s) so that the complete causal structure could be represented to help identify the most effective interventions by population. Fourth, the intervention (or exposure) and mediating mechanism(s) represent causal factors; however, the background factors (S-variables) determining relevance in a population are indicators of vulnerability. For example, skin tone, ethnicity, eye color, or hair color might all be adequate to identify the populations most likely to benefit from a sunscreen intervention. If the S-variable was another causal factor impacting the mechanism, it would create a collider. Finally, EMM as mediation by mechanism(s) whose relevance varies between populations is related to mediation analysis. However, mediation analysis and EMM address different questions. Mediation analysis focuses on how much of an effect goes through a particular mechanism. EMM, as mediation by mechanism(s) whose relevance differs between populations, focuses on why effects of an intervention acting via specific mechanisms vary between populations. Mediation is addressed by assessing direct and indirect effects. EMM is addressed by identifying the population attributes that affect the relevance of the mediating factors and then using the transport formula to predict the effect of an intervention on outcome in a new population.

Rethinking EMM has important implications for how public health practitioners propose interventions, interpret causes, and infer external validity. First, it highlights that a population-level intervention should be thought of in terms of its causal mechanism(s), so that effects in new populations can be formally inferred from the relevance of these mechanism(s) to the new population. As such, the mediating mechanisms by which an intervention operates need to be clearly identified, understood, and confirmed. Second, the researcher has to determine the population attributes that make the relevance of the mediating mechanism(s) differ between populations. Third, identifying these mediating mechanisms means that researchers can predict whether associations found in one study have external validity, thus clarifying that EMM and external validity share a common underlying structure, for which formal methods exist [5]. Overall, this new conceptualization of EMM transforms EMM from a concept that violates everyday understanding of causes into an insight generating means of thinking about interventions (or exposures) in terms of their mediating mechanism(s) and corresponding population-specific background factors, which can be formally analyzed to enable effective targeting of interventions.

CRediT authorship contribution statement

Priscilla M. Lopez: Formal analysis, Writing - original draft. **S.V. Subramanian:** Writing - review & editing. **C. Mary Schooling:** Conceptualization, Writing - review & editing.

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